UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/787,295	03/16/2001	John EN Morten	P 277177	8239

26161 7590 05/19/2003

FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
MYERS, CARLA J	

ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 05/19/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/787,295	MORTEN, JOHN EN	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) *6 and 9-12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other: .

1. Applicant's election with traverse of group I, claims 1-5, 7 and 8 with respect to the polymorphism at position 2446, is acknowledged. The traversal is on the ground(s) that the restriction requirement ignores the embodiments of the claims as being limited to detecting polymorphisms at 2 or 3 or 4 or more positions. It is stated that the restriction prohibits Applicants from presenting claims limited to such embodiments. Applicants believe that by adding a new claim that requires the detection of 13 distinct polymorphisms, the restriction requirement can no longer stand. Applicants arguments and amendment have been fully considered but are not found persuasive because the restriction requirement does not limit Applicant from claiming embodiments of methods of detecting multiple polymorphisms. However, each embodiment of detecting a distinct group of polymorphisms is considered to be a distinct invention and is subject to the same restriction requirement. Accordingly, newly added claim 12 is withdrawn from consideration as being drawn to a non-elected group since the response elected the polymorphism at position 2446. Methods of detecting specific groups of polymorphisms, such as the 13 polymorphisms set forth in claim 12, are distinct from methods of detecting each individual polymorphism because the structure and function of a single polymorphism is distinct from the structure and function of a specific group of polymorphisms. Further, as written claims 1-11 do not specifically require the detection of, for example, 2 specific polymorphisms. Applicant's response fails to address why the inventions of distinct polymorphisms should be examined together and why each of these distinct polymorphisms are considered to share the same technical feature. As discussed in the previous office action, each of the polymorphisms has a distinct

chemical, structural and functional property. A search for references disclosing the polymorphism at position 2446 would not lead one to all references teaching polymorphisms at position 740, or 2273 etc. If the examiner cited art teaching a polymorphism at position 2446, does Applicant believe that the cited art would also anticipate or render obvious claims directed to the polymorphism at position 740 or 2273? Applicants response has not provided any evidence or arguments to substantiate the position that the claimed polymorphisms all share the same technical feature. Accordingly, the requirement is still deemed proper and is therefore made FINAL.

2. The pending claims have been reviewed in light of the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001.

The examiner is using the following definitions in evaluating the claims for utility.

"Specific" - A utility that is *specific* to the subject matter claimed. This contrasts with a *general* utility that would be applicable to the broad class of the invention.

"Substantial" - A utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities.

"Credible" - Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record that is probative of the applicant's

assertions. That is, the assertion is an inherently unbelievable undertaking or involves implausible scientific principles.

"Well-established" - a specific, substantial, and credible utility which is well known, immediately apparent, or implied by the specification's disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

3. 35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 101 because the claimed invention lacks a credible, substantial, specific or well-established utility.

The claims are drawn to methods for diagnosing a nucleotide polymorphism and nucleic acids comprising a polymorphism at position 2446. The claimed nucleic acid is also not supported by a substantial utility because each of the utilities disclosed in the specification requires performing further research and does not constitute a real-world use. The specification teaches that the 2446 polymorphism causes an amino acid change of a Thr to a Met at amino acid position 679 of the α_4 integrin subunit protein. However, the specification does not teach how this alteration effects the function of α_4 integrin subunit protein. The specification (page 3) teaches that the polymorphisms can be used to identify patients most suited to therapy with a pharmaceutical compound. However, the specification has not established that the 2446

polymorphism is associated with any pharmacological properties. The specification (page 5) suggests that individuals who carry particular polymorphisms may exhibit differences in their ability to regulate protein biosynthesis and may display different abilities to respond to diseases. However, the specification has not provided any evidence to show that the 2446 polymorphism alters an individuals ability to regulate protein biosynthesis or to respond to disease. The specification has not clearly taught an association between the disclosed α_4 integrin subunit protein 2446 polymorphism and the occurrence of any disease or clinical state. Therefore, it is clear that further research would be required to practice the claimed methods and to use the disclosed polymorphisms because this would require identifying a disease which is correlated with the presence of the 2446 polymorphism. The use of the claimed method to search for diseases that are correlated with the α_4 integrin subunit protein 2446 polymorphism constitutes a research use only and does not constitute a "real world" context of use. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids containing the polymorphism at position 2446. As stated in Brenner v. Manson, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966) " a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion".

The specification (page 14) further contemplates that the 2446 polymorphism may be used for mapping, homology searching, or pharmacogenetic or bioinformatic analysis. However, this utility is characteristic of all polymorphisms and is not considered to be a specific and substantial utility. Additionally, the specification suggests that the polymorphisms can be used for

genotyping or haplotying (page 16). However, the concept of analyzing a gene for a polymorphism to assign an individual to a genotype or haplotype is considered to be a general use and is also not considered to be a substantial, specific utility. It is further noted that claims 1-4 require determining the status of the human by reference to a polymorphism. Yet, the claims do not clarify what type of status is to be determined. For example, it is not clear as to whether the status refers to the status of an individual with respect to a disease state or with respect to the fact that the individual has a particular genotype or haplotype. In either event, there are no teachings in the specification as to how to use the information of the status of a human in a meaningful manner and without extensive experimentation.

The use of a nucleic acid to discover its biological activities or properties does not constitute a specific, substantial utility. All of the biological properties of a nucleic acid need not be known to obtain a patent, but there must be at least one known specific and substantial activity or function. The further characterization of a nucleic acid containing a polymorphism is part of the act of the invention and until it has been undertaken, Applicant's claimed invention is incomplete. Because there is no specific and substantial utility for the claimed invention, credibility cannot be assessed. Accordingly, the claimed invention is not supported by either a specific or substantial asserted utility or a well-established utility. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

4. Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial, or credible asserted

utility or well-established utility for the reasons set forth above, one skilled in the art would not know how to use the claimed invention.

5. Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-5, 7 and 8 are indefinite over the recitation of "EMBL ACCESSION NO" because it is not clear as to what is encompassed by this phrase. The sequences listed in an EMBL database are continuously updated and modified. For example, the listing for Accession No. L12002 has been changed at least 3 times since it was first disclosed in July 23, 1995 (see the attached NCBI Sequence Revision History). Therefore, there is no single, constant definition for the sequence presented as EMBL Accession No. L12002, L2609 or M26841. It is suggested that the claims be amended to refer to the position of the polymorphism relative to the start site, to the extent that this is supported by the specification or use a numbering scheme relative to a specific nucleotide sequence provided in a sequence listing.

Claims 1-5, 7 and 8 are indefinite over the recitation of "the positions" because this phrase lacks proper antecedent basis because the claims do not previously refer to positions in the stated EMBL Accession No.

Claims 1-4 are indefinite and confusing because it is not clear as to what is intended to be encompassed by method for diagnosing a single nucleotide polymorphism and it is not clear as to how the stated method steps result in the diagnosis of a single nucleotide polymorphism. While

the phrase "diagnosing a disease" is conventional in the art, it is unclear as to what is intended to be encompassed by diagnosing a polymorphism. For example, it is unclear as to whether this is intended to refer to methods for detecting a polymorphism or if the concept of "diagnosing a polymorphism" is intended to characterize the polymorphism with respect to its association with disease or with some other unstated property. Further, the claims are drawn to methods for diagnosing a polymorphism, yet recite a final step of determining the status of a human by reference to a polymorphism in the α_4 integrin gene. Therefore, it is unclear as to whether the claims are intended to be limited to methods for diagnosing a polymorphism or methods for determining the status of a human. Furthermore, the claims are indefinite and unclear over the recitation of "status of a human" because the claims do not define what is intended to be meant by "status" and the claims do not clearly set forth how the "status of a human" is determined by "reference" to a polymorphism.

Claim 5 is indefinite over the recitation of "or a fragment thereof of at least 20 bases comprising at least one polymorphism" because it is not clear as to whether the polymorphism is the same as the recited polymorphism (i.e., the polymorphism at position 2446) or if the polymorphism may be any polymorphism/

Claims 7 and 8 are indefinite over the recitation of "capable of detecting" because capability is a latent characteristic and the claims do not set forth the criteria by which to determine capability. That is, it is not clear whether the recited primers and probes have the

potential to detect or do in fact detect the α_4 integrin polymorphism. Amendment of the claim to read e.g. "...primer which detects" and "....probe which detects" would obviate this rejection.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 5, 7 and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Szabo (Molecular Immunology (1995) 32: 1453-1454; cited in the IDS as reference "MR").

Szabo et al teaches the sequence of the α_4 integrin subunit gene (see figure 1) and primers useful for amplifying this gene (page 1453). Szabo further teaches cloning the α_4 integrin subunit cDNA, determining the sequence of the α_4 integrin subunit cDNA, and comparing the sequence to published α_4 integrin subunit sequences to thereby identify polymorphisms int eh α_4 integrin subunit cDNA. The method of Szabo identified the presence of a C nucleotide at position 2446 of the α_4 integrin subunit cDNA (see Figure 1). It is noted that the recitation in claims 1-3 of "determining the status of a human by reference to polymorphisms in the α_4 integrin subunit gene" is considered to encompass determining whether the individual has a wild-type gene or a modified gene. Accordingly, the method of Szabo is considered to anticipate the claimed method of diagnosing a single nucleotide polymorphism since the claimed methods encompass methods of sequencing the α_4 integrin subunit gene. With respect to claim 5, this claim has been interpreted as including any nucleic acid of at least 20 nucleotides containing any polymorphism. Claim 5 also

recites the phrase "or a complementary strand" but does not state a specific level of complementarity (e.g. 100%, 90%) and thereby includes nucleic acids having any level of sequence complementarity with the stated sequences. Furthermore, the claims require that the nucleic acids comprise a polymorphism, e.g. a "C" or a "T" but do not clearly define the sequences surrounding the polymorphism. Accordingly, claim 5 reads on the α_4 integrin subunit gene disclosed by Szabo. Claims 7 and 8 are drawn to allele specific primers and probes. However, the claims do not define the allele that the primers and probes are specific to. The reverse primer of Szabo is considered to be allele specific because they hybridize to an allele of the α_4 integrin subunit gene and are capable of indirectly detecting the stated 2446 polymorphism since the primer can amplify sequences of the α_4 integrin subunit gene containing the 2446 polymorphism. Furthermore, the α_4 integrin subunit sequence disclosed by Szabo is considered to be an allele specific probe because it hybridizes to a specific allele of α_4 integrin subunit gene and it can be used to detect polymorphisms in α_4 integrin subunit gene by, for example, SSCP. The sequence of the α_4 integrin subunit gene also has the property of being useful as a primer since it can be extended at its 3' terminus in a primer extension reaction.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made

Claim 4 is rejected under 35 U.S.C. 103(a) as being unpatentable over Szabo in view of Uhlen.

Szabo et al teaches the sequence of the α_4 integrin subunit gene (see figure 1) and primers useful for amplifying this gene (page 1453). Szabo further teaches cloning the α_4 integrin subunit cDNA, determining the sequence of the α_4 integrin subunit cDNA, and comparing the sequence to published α_4 integrin subunit sequences to thereby identify polymorphisms int eh α_4 integrin subunit cDNA. The method of Szabo identified the presence of a C nucleotide at position 2446 of the α_4 integrin subunit cDNA (see Figure 1). It is noted that the recitation of "determining the status of a human by reference to polymorphisms in the α_4 integrin subunit gene" is considered to encompass determining whether the individual has a wild-type gene or a modified gene. Szabo identified polymorphisms in the 3' and 5' untranslated regions and one polymorphism in the coding region. Szabo does not teach determining the nucleotide sequence by performing mini-sequencing.

Uhlen (see, for example, columns 11 and 12) teaches the method of mini-sequencing wherein a DNA sequence is amplified; one strand of the amplified DNA is immobilized onto a solid support; the non-immobilized strand is removed; a primer is annealed to the immobilized strand of DNA adjacent to a target position; each of four aliquots of immobilized single stranded DNA is subjected to a polymerase chain reaction, such that each aliquot has only one of the 4 possible dideoxynucleotides and contains all 4 deoxyribonucleotides; the primer/ immobilized DNA complex is subjected to an extension reaction such that when the dideoxynucleotide is incorporated into the DNA, the extension reaction is stopped; and the sequence of the DNA is

determined based upon the incorporation of the dideoxynucleotide. Uhlen (column 4) teaches that this method is simple and rapid and can be easily automated.

In view of the teachings of Uhlen, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Szabo so as to have determined the sequence of the α_4 integrin subunit gene by performing mini-sequencing in order to have provided an equally effective means for determining the sequence of the α_4 integrin subunit gene and for identifying polymorphisms in the α_4 integrin subunit gene.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (703) 308-2199. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703)-308-1119. Papers related to this application may be faxed to Group 1634 via the PTO Fax Center using the fax number (703)-872-9306 or (703)-872-9307 (after final).

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Carla Myers

May 5, 2003

CARLA J. MYERS
PRIMARY EXAMINER